From the

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

SCHAEFER, Konrad Schaefer & Emmel Gehölzweg 20 D-22043 Hamburg ALLEMAGNE PATENTANWÄLTE SCHAEFER & EMMEI EING. 10. Juni 1999 REC 11.6 FRIST

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)

Date of mailing (day/month/year)

0 8, 86, 99

Applicant's or agent's file reference 01110eppc

International application No. PCT/EP98/00917

International filing date (day/month/year) 18/02/1998

Priority date (day/month/year)

IMPORTANT NOTIFICATION

21/02/1997

Applicant

KANTON ZURICH et al.

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant	0.01.00	anta fila rafaransa		
01110e	_	ent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
Internatio	nal app	lication No.	International filing date (day/month	th/year) Priority date (day/month/year)
PCT/EF	98/00	917	18/02/1998	21/02/1997
C12N1	5/70		tional classification and IPC	1
KANTO	N ZU	RICH et al.		
and	is tran	smitted to the applicant a	according to Article 36.	d by this International Preliminary Examining Authority
2. This	HEPC	OHI consists of a total of	8 sheets, including this cover s	sheet.
	been a (see F	amended and are the bas	sis for this report and/or sheets on the Administrative Instruction	he description, claims and/or drawings which have containing rectifications made before this Authority ions under the PCT).
3. This	report	contains indications rela	ating to the following items:	
1	\boxtimes	Basis of the report		
11		Priority		
118	\boxtimes	Non-establishment of o	pinion with regard to novelty, inv	ventive step and industrial applicability
IV	☒	Lack of unity of invention	on	
V	⊠		nder Article 35(2) with regard to one suporting such statement	novelty, inventive step or industrial applicability;
VI	\boxtimes	Certain documents cité	ed	
VII		Certain defects in the in		
VIII	⊠	Certain observations or	n the international application	·
Date of su	bmissio	on of the demand	Date of c	completion of this report
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/00917

ı.	Bas	sis of the report	
1.	res	ponse to an invitation	rawn on the basis of (substitute sheets which have been furnished to the receiving Office in on under Article 14 are referred to in this report as "originally filed" and are not annexed to o not contain amendments.):
	Des	scription, pages:	
	1-4	3	as originally filed
	Cla	ims, No.:	
	1-3	9	as originally filed
	Dra	wings, sheets:	
	1/9-	9/9	as originally filed
2.	The	amendments have	e resulted in the cancellation of:
		the description,	pages:
		the claims,	Nos.:
		the drawings,	sheets:
3.			en established as if (some of) the amendments had not been made, since they have been beyond the disclosure as filed (Rule 70.2(c)):
١.	Add	litional observations	s, if necessary:
II.	Nor	n-establishment of	opinion with regard to novelty, inventive step and industrial applicability
			e claimed invention appears to be novel, to involve an inventive step (to be non-obvious), able have not been examined in respect of:
		the entire internation	onal application.
	Ø	claims Nos. 18, 19	, 34.

because:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/00917

		the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (<i>specify</i>):
	_	un annual de la contraction de
	Ø	the description, claims or drawings (indicate particular elements below) or said claims Nos. 18, 19, 34 are so unclear that no meaningful opinion could be formed (specify):
		see separate sheet
		the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
		no international search report has been established for the said claims Nos
IV	. Lac	k of unity of invention
1.	In re	esponse to the invitation to restrict or pay additional fees the applicant has:
		restricted the claims.
		paid additional fees.
		paid additional fees under protest.
		neither restricted nor paid additional fees.
2.	⊠	This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3.	This	s Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
		complied with.
	Ø	not complied with for the following reasons:
		see separate sheet
4.		nsequently, the following parts of the international application were the subject of international preliminary mination in establishing this report:
	×	all parts.
		the parts relating to claims Nos

- V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- 1. Statement

Novelty (N)

Yes:

Claims 2, 8-13, 15-17, 21, 24-27, 29-33, 35-39

No:

Claims 1, 3-7, 14, 20, 22-23, 28

Inventive step (IS)

Yes:

Claims 2, 8-11, 15-17

No:

Claims 1, 3-7, 12-14, 20-33, 35-39

Industrial applicability (IA)

Yes:

Claims 1-35, 37, 39

No: Claims

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Item III.

Claims 18, 19 and 34 are of such unclear nature that their examination for novelty, inventive step and industrial applicability is virtually impossible.

N.B.: Even if claim 34 was to read "A method...22 and 23 is used" the claim would still not be clear since no immunological detection of a disease-specific PrP (i.e. a protein) can be obtained when said protein is treated with a recombinant prion protein (i.e. another protein).

Item IV.

The application lacks unity within the meaning of Rule 13 PCT for the following reasons.

The separate inventions/groups of inventions are based on the subject-matter of:

- claims 8 and 15,
- claims 9 and 16,
- claims 10 and 17.

The common concept linking together independent claims 8-10 and 15-17 is the following:

Monoclonal antibodies (and the corresponding hybridoma cell lines) reacting with certain epitopes of PrP. This common concept is not novel, see e.g. document D1 which discloses such mABs.

Thus, said groups of inventions are not so linked as to form a single general inventive concept. No technical relationship which finds expression in the claims in terms of the same or corresponding special technical features (i.e. the particular technical feature(s) that define a contribution over the prior art) exists between these three groups of inventions.

Even if the method of preparing the hybridoma cell lines (e.g. a method according to claim 25) was inventive, the lack of unity objection would be maintained since the hybridoma cell lines per se would still not be linked so as to form a single general inventive concept.

Item V.

Reference is made to the following documents:

D1: KASCSAK et al., Dev. Biol. Stand., 80, 1993, pp.141-151.

D2: KRASEMANN et al., J. Immunological Methods, 199(2), 1996, pp.109-118.

1) Document D1 discloses (see in particular pages 142 and 143) monoclonal antibodies (3F4, 4B4 and 7G5) having the same features as those mentioned for the monoclonal antibodies according to claims 1 and 3-7. Thus, D1 destroys the novelty (Article 33.2 PCT) of claims 1 and 3-7.

Said monoclonal antibodies are produced by hybridoma cell lines (see D1, page 142, "Antisera"). This destroys the novelty of claim 14 when it refers to claims 1 and 3-7.

The methods for production of said antibodies and hybridoma cell lines as disclosed in claims 24-27 merely involve classical technics which are obvious for the skilled person. Claims 24-27 lack an inventive step under Article 33.3 PCT.

The attention of the Applicant is drawn to the following point. The method of claim 25 involves the use of a recombinant PrP according to claim 22 or 23. The fact that the PrP is defined as being "recombinant" does not per se confer to said PrP any distinguishing technical features over the naturally occurring (native) protein. If inventive step of the method of claim 25 should be based on the use of a recombinant protein, the technical features (if any) which characterise such a recombinant PrP should be introduced in the claim.

Dependent claim 12 does not contain any features which, in combination with the features of claim 1 to which it refers, meet the requirements of the PCT in respect inventive step (Article 33.3 PCT).

An antibody raised against the binding region (idiotype) of a known antibody (according to claim 1) is routinely obtained and does not involve an inventive step. Thus, claim 13 does not fulfil the requirements of Article 33.3 PCT when it refers to claim 1.

INTERNATIONAL PRELIMINARY Inter EXAMINATION REPORT - SEPARATE SHEET

II) The recombinant expression vectors disclosed in Fig.3 of D2 destroy the novelty of claims 20 and 28.

The PrP ORF was known in the art at the priority date of the present application. Its insertion in the known pET11a vector to obtain pbPrP3 (see the description page 28) does not involve an inventive step. Thus, claim 21 does not fulfil the requirements of Article 33.3 PCT.

Fig. 1 of D2 destroys the novelty (Article 33.2 PCT) of claims 22 and 23.

Claim 29 is not inventive since it merely claims the use of a known expression vector for the production of a known protein encoded by said vector.

III) It would seem that the present application is based on a monoclonal antibody, named 15B3, that can discriminate between the normal (PrPc) and disease-specific (PrPsc) forms of PrP. In the native state, mAB 15B3 stains only bovine PrPsc and not PrPc (page 11 and Fig.6b of the application). mAB 15B3 precipitates only PrPsc from infected cattle, mice or humans, but not PrPc (page 33). mAB 15B3 involves an inventive step (Article 33.3 PCT). Although mABs 6H4 and 34C9 do not exhibit this conformational epitope specificity for PrPsc, they were also not derivable in an obvious manner from the cited prior art. However, they do not show a common inventive concept with the mAB 15B3 (see item IV).

In consequence, the subject-matter of claims 2, 8-11, 15-17 fulfil the requirements of Article 33.2 and 3 PCT.

- IV) Claim 30-33 and 35-39 relate to classical test kit, immunological detection procedure, pharmaceutical preparation, method for therapy and use of mAB. Said claims are objected to for lack of novelty and/or lack of inventive step when they do not refer to novel and inventive matter (i.e. the specific mABs according to the present application).
- V) For the assessment of the present claims 36 and 38 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example,

EXAMINATION REPORT - SEPARATE SHEET

does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VI.

Certain published documents (Rule 70.10)

Application No.	Publication	Filing	Priority
WO 07/40505	00 00 07	12.00.06	14.09.95
WO 97/10505	20.03.97	13.09.96	14.09.95

Item VIII.

The subject-matter of a great many claims do not fulfil the requirements of Article 1) 6 PCT taken in conjunction with Rule 6.3a PCT which states that the subjectmatter for which protection is sought must be defined in terms of the technical features of the invention.

The claims objected to are inter alia claims 1-7, 12-14.

Note that these claims (in particular claim 2 which is considered novel and inventive) do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is defined in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

2) Article 6 PCT requires that the claims shall be clear. The mAB designations 6H4, 34C9 and 15B3 (claims 8-11) and the plasmid designation pbPrP3 used in claim 7 are arbitrary denominations which are meaningless for third parties since they convey no technical information to the reader of the claims.

The received Other reserved, -PCT International Application No. REQUEST International Filing Date The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty. Name of receiving Office and "PCT International Application" Applicant's or agent's file reference 01110eppc (if desired) (12 characters maximum) Box No. I TITLE OF INVENTION Immunological Detection of Prions. Box No. II APPLICANT Name and address: (Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.) This person is also inventor. Telephone No. Kanton Zürich vertreten durch die Erziehungsdirektion Facsimile No. CH-8090 Zürich Teleprinter No. State (i.e. country) of nationality: State (i.e. country) of residence: This person is applicant for the purposes of: all designated States except the United States of America all designated the United States of America only States the States indicated in the Supplemental Box Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.) This person is: Korth, Carsten applicant only Lengstraße 70 applicant and inventor CH-8008 Zürich inventor only (If this check-box is marked, do not fill in below.) State (i.e. country) of nationality: State (i.e. country) of residence: This person is applicant all designated all designated States except the United States of America for the purposes of: the United States of America only the States indicated in the Supplemental Box Further applicants and/or (further) inventors are indicated on a continuation sheet. Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: common representative Name and address: (Family name followed by given name: for a legal entity, full official designation The address must include postal code and name of country.) Telephone No. 040 6562051 Schaefer, Konrad Schaefer & Emmel Facsimile No Gehölzweg 20 D-22043 Hamburg 040 6567919 Teleprinter No

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Continuation of Box No. 111 FURTHER APPLICANTS A	AND/OR (FURT	 HERO IN	VENTORS
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Stierli, Beat Alte Landstraße 38			applicant only
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Streit, Peter Scheuchzerstraße 9			applicant only
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Oesch, Bruno Haldenstraße 13			applicant only
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Moser, Markus			applicant only
Waidfussstraße 25 CH-8037 Zürich			X applicant and inventor
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Further applicants and/or (further) inventors are indicated on	another continuat	ion sheet	

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addit	ion t	o the designations made above, the applicant als	o makes	unde	Rule 4.9(b) all designations which would be permitted
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Sheet No. Box No. VI PRIORITY CLAIM Further priority (Jame) are indicated in the Supplement d. Bere. The priority of the following earlier application(s) is hereby claimed In which or for which the Office of filing tools for regional or international applications Filing Date application was filed; (day/munth/year) item (1) EP 21.02.1997 European 97102837.8 Patent Office itcm (2) item (3) Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office to fee may be required): The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): Box No. VII INTERNATIONAL SEARCHING AUTHORITY Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA L Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search correquest either by reference to the relevant application (or the translation thereof) or by reference to the search request: Box No. VIII CHECK LIST This international application contains This international application is accompanied by the item(s) marked below: the following number of sheets: separate signed 1. request 5. X fee calculation sheet 4 sheets power of attorney 2. description: 43 sheets copy of general separate indications concerning deposited microorganisms 3. claims power of attorney 4 sheets 4. abstract 1 statement explaining sheets nucleotide and/or amino acid sequence listing (diskette) 5. drawings lack of signature 9 sheets priority document(s) identified in Box No. VI as item(s): other (specify): Total: 61 sheets See attached list I Figure No. of the drawings (if any) should accompany the abstract when it is published. Box No. IX SIGNATURE OF APPLICANT OR AGENT Nest to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request). Patentanwalt Konrad Schaefer - For receiving Office use only. Date of actual receipt of the purported international application: 2. Drawings: Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: received: Date of timely receipt of the required corrections under PCT Article 11(2): International Searching Authority ISA / not received: Transmittal of search copy delayed until search fee is paid

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FEE CALCULATION SHEET Annex to the Request	International application No
Applicant's or agent's file reference 01110eppc	Date stamp of the receiving Office
Applicant Kanton Zürich vertreten durch die Erziehun	
CALCULATION OF PRESCRIBED FEES 1. TRANSMITTAL FEE 2. SEARCH FEE International search to be carried out by (If two or more International Searching Authorities are competent in relat application, indicate the name of the Authority which is chosen to carry out the INTERNATIONAL FEE Basic Fee The international application contains 61 sheets. first 30 sheets 80	200, T 2200, S tion to the international international search.) 10, b ₁ 9, b ₂ 1389, B 2024, D 3413, I the the the body. coupons coupons other (specify):
Is hereby authorized to charge any deficiency deposit account.	or credit any overpayment in the total fees indicated above to my
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orm PCT/RO/101 (Annex) (January 1996; reprint January 1998)	Signature

ional Application No

PCT/EP 98/00917 CLASSIFICATION OF SUBJECT MATTER 26 6 C12N15/70 C07K IPC 6 C07K16/18 C12N5/20 CO7K14/47 C12N15/06 C12N1/21 C12N5/10 G01N33/577 G01N33/68 A61K39/395 According to international Patent Classification (IPC) or to both national classification and IPC Minimum documentation searched iclassification system followed by classification symbols: IPC 6 C07K Documentalion searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and | where practical | search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No X.0 C. KORTH ET AL.: "Characterization of 1-7.native and recombinant prion protein 32 - 34isoforms by differential exposure of antibody epitopes." SOCIETY FOR NEUROSCIENCE, ABSTRACTS, vol. 22, no. 1-3, 16 - 21 November 1996. page 2159 XP002036864 see abstract 844.3 X R. KASCSAK ET AL.: "The role of 1-7.antibodies to PrP in the diagnosis of 32-34 transmissible spongiform encephalopathies." DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, vol. 80, 1993, BASEL pages 141-151, XP002036865 see the whole document -/--Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents T* later document published after the international filing date "A" document defining the general state of the art which is not considered to be of particular relevance. or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention earlier document but published on or after the international filing date "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another involve an inventive step when the document is taken alone citation or other special reason (as specified) "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the "O" document referring to an oral disclosure, use, exhibition or document is combined with one or more other such docuother means ments, such combination being obvious to a person skilled document published prior to the international filing date but later than the priority date claimed in the art "&" document member of the same patent family Date of the actual completion of theinternational search Date of mailing of the international search report 1 5, 07, 1998 26 June 1998 Name and mailing address of the ISA

Form PCT/ISA/210 (second sheet) (July 1992)

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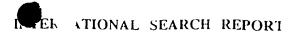
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PST/EP 98/00917

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P . X	C. KORTH ET AL.: "Prion (PrPSc)-specific epitope defined by a monoclonal antibody." NATURE, vol. 390, no. 6655, 6 November 1997, LONDON, GB, pages 74-77, XP002069611 see the whole document	1-8, 10-12, 14,15, 17-39
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INTERNATIONAL SEARCH REPORT

ational application No PCT/EP 98/00917

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
, and the state of
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 36 and 38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). Box II Observations where units of investigations is the second and third sentences.
Box II Observations where unity of invention is lacking (Continuation of Item 2 of Iirst sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest No protest accompanied the payment of additional search fees.



!ONAL SEARCH REPORT

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